EXHIBIT 2

Lee-Jen Wei, Ph.D.
Professor of Biostatistics
Harvard University

Report on Statistical Analysis of Use of Dietary and Occupational Studies to Infer Relationship Between NDMA and NDEA Impurities in Valsartan and Cancer

A. Introduction

1. This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions[1] I have offered in this report is given to a reasonable degree of scientific certainty and is based on scientific methods and procedures, the materials I have reviewed in connection with this litigation, as well as my education, training, knowledge, and experience. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I also reserve the right to respond to and rebut all information provided in discovery, which I understand is ongoing, and any opinions offered by Plaintiffs' experts at their depositions or at trial.

[1] This report contains my opinions applicable to questions of general causation only. This report is not intended to be an exhaustive recitation of all of my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

2. Citations to specific reference material are also offered in this report, where I believe it necessary to cite a specific source. Otherwise, my opinions are derived from a combination of reference sources and my own scientific knowledge. This report is not meant to be an exhaustive recitation of all of my opinions as I understand my opinions will be more fully explored at my deposition. My curriculum vitae, detailing my education, experience, and list of the publications I have authored, is attached to this report as Exhibit A.

3. A list of materials that I considered in rendering the opinions offered in this report is attached as Exhibit B. Because I have reviewed ample medical, regulatory, and scientific literature over my continued education in my field of expertise, it is not possible to list all of the material informing my opinions. I am, however, attaching a list of references that I have reviewed in Exhibit B. By including literature on this list, it does not imply that I place any particular emphasis on the reference or that I agree with all of the content in any particular publication.

4. At the time of trial, I may use other records or graphics to assist with the illustration of my opinions. I reserve the right to amend and further supplement my opinions based on additional material provided to me after the date of this report.

5. I may use at trial any exhibits as a summary or in support of all of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by the plaintiff's experts, or other witnesses; (5) the individual plaintiff's records; and (6) any exhibit used in or identified at any deposition take in this Litigation. If further data becomes available, I will be happy to review it and consider whether to modify any portion of these opinions.
6. I have been compensated at the rate of $500 per hour for my work on this matter. I have no conflicts of interest to disclose.
7. I have testified as an expert witness at deposition in one matter in the past four years: *In re Taxotere (Docetaxel) Products Liability Litigation*, MDL No. 2740 (E.D. La.).

B. Qualifications

8. I received a Ph.D. in Statistics in 1975 from the University of Wisconsin. I have been a tenured professor of biostatistics at Harvard University since 1991 and was a professor of biostatistical science and computational biology at Dana-Farber Cancer Institute, Harvard Medical School between 1997 and 2012. I was the scientific director for the Program of

Quantitative Sciences for Pharmaceutical Medicine and the co-director of the bioinformatics core at Harvard School of Public Health from 2003 to 2007. From 2003 to 2004, I served as the acting chair of the department of biostatistics at Harvard University. I was a tenured full professor of biostatistics and statistics at University of Wisconsin, University of Michigan, and George Washington University from 1982 to 1991.

9. Throughout my career, I have been intimately involved in the design, monitoring, and analysis of clinical studies, including for pharmaceuticals. I have served on numerous Data and Safety Monitoring Boards for clinical trials and have extensive experience in the evaluation of efficacy and safety data from clinical studies. I have long been actively involved in clinical research and development of a number of novel quantitative methods for analyzing data readily applicable to clinical studies.

10. My scholarly research includes over 230 publications in peer-reviewed journals. I am responsible for developing numerous novel statistical methods for designing, monitoring, and analyzing clinical studies, survival analyses, and meta-analyses. Many of these methods have been included in the most commonly used statistical software packages such as SAS, S-plus, and R. I have served on the editorial boards of a number of

statistical journals and am an elected Fellow of the American Statistical Association and Institute of Mathematical Statistics. I was named "Statistician of the Year" in 2007 by the Boston Chapter of the American Statistical Association. In 2009, I received the Wilks Medal from the American Statistical Association, one of the most prestigious awards in the field of statistics, for outstanding contributions to clinical trial methodological research.

C. Assignment

11. I have been retained by Defendants to provide an expert opinion in the litigation styled *In re: Valsartan Products Liability Litigation*, MDL No. 2875 (D.N.J.). Specifically, I was asked by counsel for Defendants to review and assess the opinions presented by David Madigan, Ph.D. who submitted an expert report on behalf of the Plaintiffs analyzing the results from the dietary and occupational studies to infer potential risk of carcinogenicity of NDME or NDEA impurities in Valsartan, and to provide my own assessment of those issues.

D. Executive summary

12. I disagree with the opinions, analysis and conclusions in Dr. Madigan's report; we cannot justify extrapolating the results from the dietary and

occupational studies to the patient population who took the Valsartan containing NDMA.

13. To claim a potential cancer risk via the dose response profile for NDMA using a "statistical significance" criterion (p-value < 0.05) is strongly discouraged by the American Statistical Association. Such a statistical claim does not have a clear clinical interpretation.

14. Even with the above artificial criterion to claim there is a dose response profile, one needs to make multiple adjustments for the p-values. In Dr. Madigan's report, there were at least 152 comparisons. Thus, the threshold value to define the so-called "statistical significance" is 0.0003, not 0.05, for each individual statistic test. Most tests for which Dr. Madigan claimed to be "statistically significant" would not be significant anymore with this threshold.

15. All the studies cited by Dr. Madigan in the report are observational. The observational studies heavily depend on the validity of modeling for adjusting the baseline imbalance between two groups to be compared. If these model assumptions are not met, the conclusions can be misleading. Moreover, the analysis and design of those dietary and occupational studies cannot support a causal relationship of cancer and valsartan. At best, they serve as a hypothesis generating vehicle. Without further well-

conducted, observational studies, conclusions about the potential connection between NDMA impurities in Valsartan and cancer are unreliable.

16. Based on my assessment of the dietary and occupational studies assessing the risk of cancer from NDMA, these studies fail to demonstrate a risk of cancer from Valsartan.

E. Statistical Analysis and Issues of Comparative Observational Studies for Assessing Exposure Effects

17. Suppose that we are interested in the rate of occurrence of a certain clinical event (for example, cancer) among subjects exposed to NDMA or NDEA to their counterparts (control). In the first step, we take a sample from a population of subjects exposed and another sample from the population of subjects who were not exposed. Assuming that these samples are valid representatives of the two populations, quantitative/analytic methods can be used to determine whether the exposed group has higher, lower or similar event rate than that for the control group. Since we draw conclusions based on a subset of subjects, any qualitative or quantitative interpretation of the result (i.e., whether the rate is higher or not) is subject to sampling error. That is, the observed event rate may be higher (leading to a possible false positive finding) or

lower (leading to a possible false negative finding) than the true event rate in the population. An efficient statistical method for analyzing such data minimizes the chance of making these two types of errors. It is important to note that except for the exposure to NDMA or NDEA, the exposed subjects in the sample should be similar to the subjects in the non-exposed sample with respect to important observable or unobservable confounders. Any imbalance with respect to those factors can seriously obscure the analysis results and results in invalid conclusions on the exposure effects.

18. After we have determined how to draw a valid sample from the population of interest, one has to determine what clinical endpoints are most appropriate to quantify the exposure effect. For the present legal case, the endpoint is whether the subject had a certain type of cancer or the time to occurrence of cancer. Suppose that based on a sample of 100 patients at the end of study, four patients experienced such events. An obvious estimate of the event rate for the underlying population is 0.04 (or 4%). This is called a point estimate. However, this estimate is based on a sample of patients. The true event rate for the entire population may be more or less than 4%. Different studies generating different samples may find a different proportions of subjects with cancer. Therefore, when

observing results from a single sample, it is important to attach a level of confidence to the observed point estimate. This quantitative, scientific process is called "drawing or making inferences" about the true event rate. For comparing the exposed and control groups, in the report by Dr. Madigan, the 95% confidence interval, and the p-value (whether less or greater than 0.05) were utilized to claim the exposure effect would be "statistically significant," which was repeatedly used in the report.

19. Let me turn to the issues of comparing two groups of subjects, one having been exposed and the other being in the control. To make sure that two samples of subjects are comparable with respect to all potential confounders, we often rely on a randomized clinical trial setting. Such a clinical study yields a well-designed experiment that has the potential for generating reliable prospective data on safety. Such studies are conducted and monitored according to a pre-specified protocol, which details the exposure administered (e.g., form, dosage, frequency), the clinical or biological endpoints (e.g., lab value, patient's quality of life, time to remission, time to a toxicity event), the study patient population and other clinical and statistical considerations. The trial is usually randomized and blinded. Subjects are assigned randomly to one of the study arms and neither physicians nor patients are told whether the patient is receiving an

active exposure or a control. This avoids selection bias or other experimental bias. When appropriately designed, results from a well-conducted, randomized clinical trial are regarded as a gold standard in controlled settings to evaluate the efficacy and safety of an exposure.

20. For the present case, we cannot utilize such a gold standard approach to evaluate the exposure effect. Thus, observational studies were used for all the articles cited by Dr. Madigan. It is known that such observational studies have inherent issues in the valid assessment of the exposure since we cannot guarantee the comparability between two groups at the subjects' baseline factors. For example, most of the studies cited by Dr. Madigan compared the least and most exposed groups with respect to NDMA. It is not clear one can ensure that those groups are only different with respect the exposure levels, but not for other factors.

21. Even if we can claim we collected all the relevant patients' baseline factors, the modeling of the adjustments for those factors may be questionable since the standard lack of fit test for the model fitting does not provide clinically meaningful interpretation via a p-value of the test. For example, in a publication Dr. Madigan heavily cited in his report, Loh

et al.[2] claimed that dietary NDMA intake was significantly associated with increased cancer risk in men and women via Cox proportional regression adjusted for age, sex, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women). However, it is not clear a thorough model fitting assessment was conducted. If the Cox model does not fit the data well, it is known that the resulting hazard ratio does not have clinically meaningful interpretation (Uno et al. 2014[3]; Pak et al. 2017[4]; Tian et al. 2018[5]). For this situation, the conclusions of the study and inferences drawn by Dr. Madigan based on the study would be invalid and inherently unreliable.

22. As another example about the adequacy of modeling, in the paper by Zheng et al.,[6] multiple logistic regression models were utilized. It is not

[2] Loh, Y. H., Jakszyn, P., Luben, R. N., Mulligan, A. A., Mitrou, P. N., & Khaw, K. T. (2011). N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study. Am J Clin Nutr, 93(5), 1053-1061. doi:10.3945/ajcn.111.012377.
[3] Uno et al. Moving Beyond the Hazard Ratio in Quantifying the Between-Group Difference in Survival Analysis, Journal of Clinical Oncology (2014) DOI: 10.1200/JCO.2014.55.2208.
[4] Pak, et al. Interpretability of Cancer Clinical Trial Results Using Restricted Mean Survival Time as an Alternative to the Hazard Ratio (2017) *JAMA Oncol*. Doi:10.1001/jamaoncol.2017.2797.
[5] L. Tian et al. Moving beyond the conventional stratified analysis to estimate an overall treatment efficacy with the data from a comparative randomized clinical study, (2018) Statistics in Medicine. DOI: 10.1002/sim.8015.
[6] Zheng, J., Stuff, J., Tang, H., Hassan, M. M., Daniel, C. R., & Li, D. (2019). Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study. Carcinogenesis, 40(2), 254-262. doi:10.1093/carcin/bgy169.

clear if the model fits the data well. Again, a lack of fit test for model fitting is not informative since it only provides a p-value. A large p-value from a test of goodness of fit does not mean the model would fit the data well since the test might not have power. On the other hand, a large study may result in a small p-value and we reject the model, which may be a good approximation to the true one. Without such analysis, the conclusions of the study and inferences drawn by Dr. Madigan based on the study would be invalid and inherently unreliable.

23. Moreover, for the papers in meta-analysis cited by Dr. Madigan, it is not clear if the authors for the individual papers in the meta-analysis had carefully checked the adequacy of the models utilized in the analysis. Without such analysis, the conclusions of the meta-analysis and inferences drawn by Dr. Madigan based on the meta-analysis would be invalid and inherently unreliable.

24. In their paper, Hidajat et al. (2019)[7] stated that "To examine the probability of dying from specific causes in a cohort with nearly complete mortality (94.1%), competing risk survival analysis was used to model

[7] Hidajat, M., et al: Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. Occup. Environ. Med. 76:250-258, 2019.

time to death either from specific cancers, a competing event (death by another cause) or censored due to attrition (such as through emigration)." Following the method by Fine and Gray, they further stated that "Subjects who experienced a competing event before the event of interest remain in the risk set and are weighted using the inverse probability of censoring weighting approach. This is in contrast to a standard Cox proportional hazard approach which would consider deaths from competing risks to be censored and would be removed from the risk set. Censoring competing events violates the assumption that censoring occurred at random and is independent from the risk of dying from the cause of death of interest, leading to a biased Kaplan-Meier estimator. Furthermore, within the context of competing risks, the interpretation of HRs from a standard Cox proportional hazard approach changes to the hazards of dying if no other deaths occurred, which is untenable in a cohort with 94.1% mortality rate. Subdistribution HRs (SHRs) are estimated using *stcrreg* in Stata V.15 and comparable in interpretation to proportional HRs in Cox models."

25. Unfortunately, using the subdistribution hazard ratio to quantify the group difference in the presence to competing risks has been criticized

(Zhao et al. 2018, JAMA-Cardiology[8]; McCaw et al. 2020, New England Journal of Medician[9]; McCaw et al. 2020, Annals of Internal Medicine[10]). Such hazard ratio has no clinical meaning. In fact, this issue was also cited by Fine and Gray (1999),[11] which was the method used by Hidajat et al in their report. Therefore, the results reported by Hidajat et al are difficult to interpret clinically. Alternative methods have been proposed in the above cited articles.

F. Extrapolation of the Results from the Diet or Occupation Studies to Infer the Exposure Issues for Valsartan Population

26. Based on the information available and the content of Dr. Madigan's report, we cannot use the results from diet or occupation studies to make an inference about the exposure effects for the population with valsartan. For example, from the meta-analysis by Song et al. regarding gastric cancer and NDMA consumption, the authors clearly stated that there was an obvious evidence of heterogeneity among studies involved, as

[8] Zhao L, Tian L, Claggett B, et al. Estimating treatment effect with clinical interpretation from a comparative clinical trial with an end point subject to competing risks. JAMA Cardiol (2018); 3: 357-8.
[9] McCaw, Zack, Kim, Dae and Lee-Jen Wei, Letter to the Editor for Remdesivir for the Treatment of Covid-19— Preliminary Report, New England Journal of Medicine (2020). DOI: 10.1056/NEJMc2022236.
[10] McCaw et al., How to Quantify and Interpret Treatment Effects in Comparative Clinical Studies of COVID-19, (2020) Ann Intern Medicine, doi:10.7326/M20-4044
[11] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc (1999), 94:496–509.

demonstrated by their use of the random effects model to deal with heterogeneity. [12] That is, the study populations in the meta-analysis are quite different and the resulting risks vary drastically across studies. Some studies suggested no exposure effects at all. For instance, the study by Knekt et al.[13] On the other hand, the study by Larsson et al. indicated issues of potential cancer risk.[14] Therefore, even for the diet consumption studies, one cannot extrapolate the results from one study to another population even within the dietary research area. Using the results from non-valsartan studies to claim issues for potential carcinogenicity of low levels of an NDMA impurity in valsartan is not scientifically valid. Based on my assessment of the dietary and occupational studies assessing the risk of cancer from NDMA, these studies fail to demonstrate a risk of cancer from Valsartan.

[12] Song, P., Wu, L., & Guan, W. (2015). Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis. Nutrients, 7(12), 9872-9895. doi:10.3390/nu7125505.

[13] Knekt, P.; Jarvinen, R.; Dich, J.; Hakulinen, T. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: A follow-up study. Int. J. Cancer (1999), 80, 852–856.

[14] Larsson, S.C.; Bergkvist, L.; Wolk, A. Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. Int. J. Cancer (2006), 119, 915–919.

G. Studies Directly Dealing with the Valsartan Impurities

27. Pottegård et al. conducted a Danish nationwide cohort study to investigate whether the use of N-nitrosodimethylamine (NDMA) contaminated valsartan products would increase the risk of cancer.[15] In the study, there were 5,150 Danish patients with no history of cancer, aged 40 years or older, and using valsartan on January 1, 2012, or initiating use between January 1, 2012 and June 30, 2017. The primary endpoint is the time to all cancers except non-melanoma skin cancer. The study used a Cox regression model with covariates adjustments. There were 3,625 participants contributed 7,344 person years classified as unexposed to NDMA, and 3,450 participants contributed 11,920 person years classified as ever exposed to NDMA.[16] There were 104 cancer outcomes among NDMA unexposed participants and 198 among exposed participants, the adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41). Moreover, there was no evidence of a dose-response relation. As such, the study suggests that there is no evidence to justify valsartan with NDMA caused cancer. The proportional hazards

[15] Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. 2018. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ 362:k3851. doi:10.1136/bmj.k3851.
[16] *Id.*

assumption was tested using Schoenfeld residuals in the paper. Various sensitivity and supplementary analyses were also conducted for supporting the robustness of the results from the primary analysis. This type of studies are more reliable for assessing the exposure effect from valsartan with NDMA than the diet and occupational studies.

28. Gomm et al. conducted a study to investigate the same issue via German health insurance data.[17] There were 780,871 persons who had filled a prescription for valsartan between 2012 and 2017 included in the study. There was no evidence on an association between exposure to NDMA-contaminated valsartan and the overall risk of cancer. There were 10 different types of cancers explored in the study. Only for liver cancer, the hazard ratio is 1.16 with a 95% confidence interval of 1.03 to 1.3.[18] However, if we apply the multiple comparison adjustment with ten cancer categories via Bonferroni adjustment, the confidence level would be 99.5%, not 95%. Therefore, the resulting confidence interval will cover 1, which indicates that there is no evidence of the association between the exposure and the liver cancer.

[17] Gomm W, Röthlein C, Schüssel K, et al. 2021. N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer—A Longitudinal Cohort Study Based on German Health Insurance Data. Deutsches Ärzteblatt international 118 (Forthcoming). doi:10.3238/arztebl.m2021.0129. Online ahead of print.
[18] *Id.*

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H. Overuse of "statistical significance" via a p-value < 0.05 as a criterion to assess the exposure effects

29. Dr. Madigan repeatedly based his conclusions about the exposure effect solely on whether the p-value was less than 0.05 or not. But the overemphasis of using p=0.05 as the cutoff for "statistical significance" has been strongly criticized by experts in the field of statistics and the American Statistical Association ("ASA"). For this reason, the ASA (the most influential and the largest statistical professional society in the world), issued a formal statement in 2016 to strongly discourage using a threshold value of 0.05 or any other arbitrary value to claim a "significance" finding.[19] The statement also emphasized that the "p-value was never intended to be a substitute for scientific reasoning."[20]

[19] Ronald L. Wasserstein & Nicole A. Lazar (2016) The ASA Statement on *p*-Values: Context, Process, and Purpose, *The American Statistician*, 70:2, 129-133, DOI: 10.1080/00031305.2016.1154108.

[20] *Id.* ("Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold. Practices that reduce data analysis or scientific inference to mechanical "bright-line" rules (such as "$p < 0.05$") for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making. A conclusion does not immediately become "true" on one side of the divide and "false" on the other. Researchers should bring many contextual factors into play to derive scientific inferences, including the design of a study, the quality of the measurements, the external evidence for the phenomenon under study, and the validity of assumptions that underlie the data analysis. Pragmatic considerations often require binary, "yes-no" decisions, but this does not mean that p-values alone can ensure that a decision is correct or incorrect. The widespread use of "statistical significance" (generally interpreted as "$p \leq 0.05$") as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process.").

30. Dr. Madigan's report repeatedly relies on a threshold value of 0.05 to claim the exposure effect on cancer risk without clinically and scientifically meaningful interpretations. Accordingly, Dr. Madigan's conclusions are not relevant to the subject matter of the present litigation.

I. Issue of using multiple statistical tests without adjustment

31. Even if we accept Dr. Madigan's criteria with a false positive rate of 0.05 as an arbitrary threshold value, this procedure was generally used to establish the so-called "statistical significance" of a result when testing a *single* clinical endpoint in a *single* study. This level can be very "liberal" (i.e., can result in statements of statistical significance when none exists) if *multiple* statistical tests and/or studies are examined simultaneously. In other words, making multiple comparisons would seriously inflate the overall "false positive" rate. For example, in the article by Zheng et al. cited in paragraph 13 of Dr. Madigan's report, in their Table 2, there were 24 comparisons for the trend tests. Using the 5% rule for claiming statistical significance to analyze simultaneously a large number of tests in a study will yield a high rate of false positive findings. Often, the overall false positive rate could be as high as 20% or more (that is, a very high chance of finding an exposure is not safe with respect to control, when, in fact, there is no difference between the two groups). This would lead to

wrong conclusions about the exposure effects. Inflated false positive rate issues have been extensively discussed, for example, in Friedman, Furberg and DeMets[21] when dealing with multiple testing or simultaneous inferences. For another article cited in Dr. Madigan's report (Goodman et al.) regarding the lung cancer, in their Table 1, there were 74 trend tests. For the comparisons for Q2, Q3 and Q4 vs Q1 (Sometimes, Dr. Madigan used the *first, second* and *third quantile*, I assume he meant quartiles) with respect to various degrees of exposures, there were 444 tests. For these cases, the false positive rates would be drastically increased and none of the comparisons would be "statistically significant."

32. A standard procedure to handle the multiple comparison issue is to use the Bonferroni adjustment. For example, if there are 50 different types of tests conducted, the total false positive rate is 5%, then for each individual test, we should use a false positive rate of 0.1% (5% divided by 50) to assess whether there is a potential signal on the safety concern. The corresponding confidence interval level should be 99.9% (100% - 0.1%). For the study by Goodman et al. The level of threshold value would be

[21] For details see Friedman, Furberg and DeMets, Fundamentals of Clinical Trials, Second Edition, Chapter 15; p. 215, Littleton, MA, 1985.

0.05/444 = 0.00011. That is, unless a p-value is less than 0.00011, one could not claim so called "statistical significance."

33. The problem of inflation of a Type I error (or false positive) rate becomes much worse when we examine the results of several independent clinical studies at the same time with a Type I error rate of 0.05 for each study. For example, suppose there are three independent studies which compare the exposure group with control. Suppose that we claim that there is a significant difference between these two groups when the p-value of any one of these three trials is less than 0.05. If we apply this decision rule, the total Type I error rate would be 14.3%; that is, even if there were no differences between the exposure and control with respect to cancer incidence, the chance of claiming either the exposed or control is harmful is more than 14.3%. This problem is compounded if we apply the same rule to a large number of studies. Therefore, when we analyze multiple studies and statistical test simultaneously, any conclusion of toxicity must be carefully interpreted due to the multiplicity of tests.

34. Since Dr. Madigan cited multiple studies with an extremely large number of statistical tests in his report, all the so-called "statistical significance" claims would not be valid using 0.05 as the threshold value for each test. In his report, from two tables presented for the dietary and occupational

studies, Dr. Madigan reported 152 test results and highlighted the "statistically significant" entries. With the multiple comparison adjustments, each test should use the critical value of 0.05/152 = 0.0003. It is not clear which entries in the tables of the occupational and diet studies would still be "statistically significant."

J. Errors and Inconsistency in Dr. Madigan's report

35. Dr. Madigan's report contains various errors. For example, regarding esophageal cancer, it stated that Cui et al. found an increased risk of such cancer risk associated with NDMA, the *hazard ratio* =1.18, and 95% CI (0.98, 1.41). In Cui paper, I cannot find such a claim with respect to hazard ratio. He then added the odds ratio results from Rogers et al. to Cui's. One cannot combine odds ratio with the hazard ratio (if Cui were using the hazard ratio as the summary measure). The odds ratio and hazard ratio are quite different summary measures for assessing the toxicity (Paragraph 12 in Dr. Madigan's report). One is using the binary outcome (yes or no for cancer) and the other using the time to occurrence of cancer.

36. Dr. Madigan added Loh's *hazard ratio* of 1.13 to Song's meta-analysis, but Song did not report hazard ratios in their article (Paragraph 10 in Dr. Madigan's report). It is not clear if we combine these two different

summary measures how to interpret such a combination and whether any conclusions inferred from this combination are valid.

K. Conclusions

37. In Paragraph #33 in the report, Dr. Madigan claimed that for NDMA, "statistically significant" increased gastric cancer risk arises at LCEs as low as 1,962 ug, the equivalent threshold for lung cancer is 4,303 ug, for esophageal cancer is 4,235 ug, and for rectal cancer is 3,343 ug. Based on the report by Dr. Madigan, those claims cannot be justified with the issues and concerns I raised in this report.

38. The same concern is applied to the claims in Paragraph #34 in Dr. Madigan's report. Moreover, those threshold values may not be transportable to the case for the contaminated valsartan without appropriate validations. Thus the risks of cancer discussed in Paragraphs 33 and 34 in Dr. Madigan's report are not scientifically justified. Based on my review of the studies discussed by Dr. Madigan the dietary and occupational studies and the NDMA levels referenced cannot be extrapolated to Valsartan with NDMA.

39. There is no statistical evidence based on studies cited by Dr. Madigan that the levels of NDMA or NDEA reported in valsartan can cause cancer. Based on my review of the studies referenced by Dr. Madigan and my

own review of his analysis, based on scientifically valid reasoning and methodology, I do not see any valid statistical support that Valsartan with NDMA or NDEA can cause cancer in patients.

Date: August 2, 2021

Lee-Jen Wei, Ph.D.

WEI

EXHIBIT A

CURRICULUM VITAE

LJ WEI

ADDRESS

Lee-Jen Wei
Department of Biostatistics Harvard University
677 Huntington Avenue
Boston, MA 02115
Phone: (617) 432-2826
E-mail address: wei@hsph.harvard.edu

EDUCATION

1970	B.S., Mathematics, Fu-Jen University, Taipei, Taiwan
1975	Ph.D., Statistics, University of Wisconsin, Madison

WORKING EXPERIENCE

2003-2004	Acting Chair Department of Biostatistics Harvard University
1997-present	Professor of Biostatical Science and Computational Biology Dana-Farber Cancer Institute
1991-present	Professor of Biostatistics Harvard University
1988-1991	Professor of Statistics and Human Oncology Associate Director of Biostatistics Center University of Wisconsin, Madison, Wisconsin
1986-1988	Professor of Biostatistics and Statistics University of Michigan; Director, Biostatistics Unit University of Michigan Cancer Center
1985-1986	Professor of Statistics George Washington University
1984-1985	Visiting Professor of Biostatistics Harvard University
1981-1984	Professor of Statistics George Washington University

1980-1981	Cancer Expert National Cancer Institute, NIH
1979-1981	Associate Professor of Statistics University of South Carolina
1975-1979	Assistant Professor of Statistics University of South Carolina

HONORS

2009	Wilks Memorial Award, American Statistical Association
2007	Mosteller Statistician of the Year (sponsored by Boston Chapter, American Statistical Association)
2001	Greenberg Distinguished Lectureship Univ. of North Carolina at Chapel Hill
1999	Distinguished Alumni Award, Fu Jen University
1993	Fellow, Institute of Mathematical Statistics
1991	A.M. (Honorary Degree), Harvard University
1988	Elected Member, International Statistical Institute
1986	Fellow, American Statistical Association
1987	Spiegelman Award for Outstanding Statistical Research in Public Health, American Public Health Association

EDITORIAL ACTIVITIES

1984-1991	Associate Editor, Journal of the American Statistical Association (Theory and Methods Section)
1993-1996	Associate Editor, Journal of the American Statistical Association (Theory and Methods Section)
2005-present	Associate Editor, Journal of the American Statistical Association (Theory and Methods Section)
1984-1988	Member of Editorial Board, Communications in Statistics (A)
1988-1996	Associate Editor, Statistica Sinica
1989-1993	Associate Editor, Biometrics
1990-2000	Associate Editor, Journal of Biopharmaceutical Statistics

PH.D. STUDENTS

Levint (1983) Nonparametric survival analysis for block designs.

C. Cowan (1984) The effect of misclassification on estimates from capture and recapture studies.

W. Johnson (1985) Combining dependent tests with incomplete repeated measurements.

S. Davis (1987) Nonparametric methods for analyzing incomplete non-decreasing repeated measurements.

Y. Lin (1989) Robust inference and goodness-of-fit tests for Cox's proportional hazards model.

J. Su (1990) Lack-of-fit tests for generalized linear models.

E. Lee (1991) Regression analysis for the correlated clustered failure time data.

J.S. Lin (1991) Analysis of multivariate survival data.

S.H. Jung (1992) Survival analysis with median regression models.

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WEI

EXHIBIT B

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation
Case No. 19-2875

LEE-JEN WEI, PHD
LIST OF MATERIALS CONSIDERED

MATERIALS CONSIDERED	BATES NOS.
MDL PLEADINGS AND GENERAL DOCUMENTS	
2019.06.17 Am. Master Personal Injury Complaint	N/A
2019.06.17 Am. Master Medical Monitoring Complaint	N/A
2020.03.13 Am. Master Economic Monitoring Complaint	N/A
2019.06.26 Confidentiality and Protective Order	N/A
2021.02.11 Letter from Lori G. Cohen to Judge Vanaskie	N/A
2021.02.11 Letter from Adam Slater Providing an Overview	N/A
EXPERT REPORTS (WITH EXHIBITS)	
2021.07.04 Report of Dr. Mahyar Etminan	N/A
2021.07.06 Report of Dr. Stephen Hecht	N/A
2021.07.06 Report of Dr. Stephen Lagana	N/A
2021.07.07 Report of Dr. David Madigan	N/A
2021.07.06 Report of Dr. Dipak Panigrahy	N/A
DISCOVERY DOCUMENTS CITED BY PLAINTIFFS' EXPERTS	
Spreadsheet of NDMA Test Results for ZHP API	SOLCO00028261
Torrent Pharmaceutical Limited – Valsartan Impact Assessment of NDMA	TORRENT-MDL2875-00133890
LITERATURE	
2017.11.00 EPA NDMA Technical Fact Sheet	N/A
All materials cited in the 2021.07.04 Report of Dr. Mahyar Etminan	N/A
All materials cited in the 2021.07.04 Report of Dr. Stephen Hecht	N/A
All materials cited in the 2021.07.04 Report of Dr. Stephen Lagana	N/A
All materials cited in the 2021.07.04 Report of Dr. David Madigan	N/A
All materials cited in the 2021.07.04 Report of Dr. Dipak Panigrahy	N/A
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Johnson, GE, et al., Nitrosamines and heme iron and risk of prostate cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2012; 21(3):547-51	N/A
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MATERIALS CONSIDERED	BATES NOS.
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McCaw, Zack, Kim, Dae and Lee-Jen Wei, Letter to the Editor for Remdesivir for the Treatment of Covid-19— Preliminary Report, New England Journal of Medicine (2020). DOI: 10.1056/NEJMc2022236	N/A
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Uno et al. Moving Beyond the Hazard Ratio in Quantifying the Between-Group Difference in Survival Analysis, Journal of Clinical Oncology (2014) DOI: 10.1200/JCO.2014.55.2208	N/A
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Zhao L, Tian L, Claggett B, et al. Estimating treatment effect with clinical interpretation from a comparative clinical trial with an end point subject to competing risks. JAMA Cardiol (2018); 3: 357-8	N/A
Zheng, J, et al., Permitted daily exposure limits for noteworthy N-nitrosamines. Environmental and Molecular Mutagenesis (07 May 2021)	N/A
Zheng J, Stuff J, Tang H, Hassan MM, Daniel CR, Li D. Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study. Carcinogenesis 2019; 40(2):254-62	N/A
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All materials cited or referenced in my expert report and attachments	N/A
This list includes items Plaintiffs' experts relied upon. By so doing, Defendants and this expert are not waiving any arguments or objections related to admissibility.	N/A